II. Remarks

A. Status of the Claims

Claims 76-84 and 88-89 are pending in this application. Claim 76 has been amended without prejudice to correct a typographical error. It is respectfully submitted that no new matter has been added by virtue of this amendment.

B. Rejection under 35 U.S.C. § 103

In the Office Action, claims 76-84 and 88-89 were rejected under 35 U.S.C. 103(a) "as being unpatentable over US Patent 5,837,379 to Chen et al. by itself or in view of Cheng et al. (Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (1993), 10:1683-1687)."

1. Rejection over Chen et al.

i.) The Applicants position with respect to genus-species is relevant to an obviousness rejection

In the Office Action, the Examiner states that "applicants arguments with regard to genus-species is not relevant to the instant rejection since the rejection has not made an anticipation rejection and rather made under obviousness."

Applicants respectfully disagree with the Examiner's position. In support of this position, the Examiner is directed to MPEP 8th Edition, Revision 4, § 2144.08, which is entitled "Obviousness of Species When Prior Art Teaches Genus" (Emphasis Added). The Examiner is further directed to MPEP 8th Edition, Revision 4, § 2144.08, Subsection II, which is entitled "Determine Whether The Claimed Species Or Subgenus Would Have Been Obvious To One Of Ordinary Skill In The Pertinent Art At The Time The Invention Was Made" (Emphasis Added). In the Applicants' responses of March 29, 2006 and

August 22, 2005, guidelines set forth in this section were analyzed to support the position that the Examiner did not establish a *prima facie* case of obviousness in view of the prior art genus. In view of the guidelines set forth in the MPEP for determining obviousness of a species in view of a prior art genus, Applicants respectfully submit that the Examiner cannot dismiss the Applicants' positions with respect to genus/species based on the statement that the rejection was "not made an anticipation rejection and rather made under obviousness." As the rejection was made under obviousness, the Applicants' positions are relevant.

Therefore, Applicants resubmit that Chen et al. is directed to controlled release dosage forms and incidentally mentions lovastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.)

Applicants respectfully submit that one skilled in the art would not be motivated to select the particular claimed species (*i.e.* lovastatin) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al. In support of this position, it is respectfully submitted that with respect to Chen et al., (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed species; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, Revision 4, § 2144.08 Subsection II (A-C). A discussion of these points follows:

(a) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or subgenus must be taught by the prior art. *See* e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215.

It is respectfully submitted that the size of the possible active agents which can be used in accordance with Chen et al. is sufficiently large as not to inherently disclose each and every individual species (e.g. lovastatin) which falls within their broad genus.

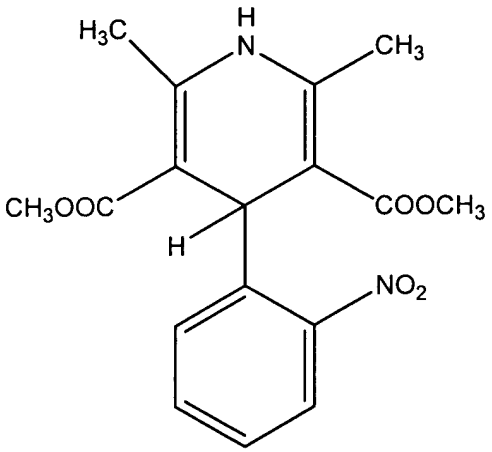
(b) The reference does not expressly teach a particular reason to select the claimed species

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, Revision 4, § 2144.08 Subsection II (A)(4)(B). It is respectfully submitted that the only recitation of lovastatin in Chen et al. is embedded within a large genus. Accordingly, Chen et al. do not expressly teach a particular reason to select lovastatin from the plethora of other possible species in the genus of the reference.

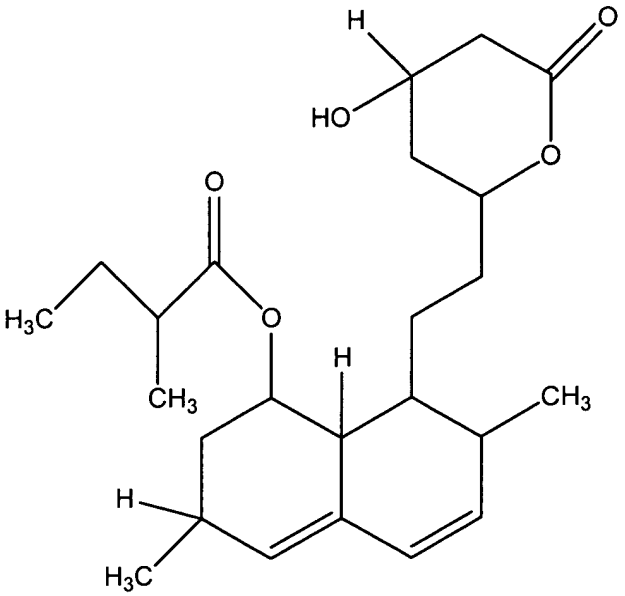
(c) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. *See*, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agent exemplified in Chen et al. is nifedipine in Examples 1 and 2.

It is respectively submitted that nifedipine is not similar in structure to lovastatin and does not provide similar pharmacological activity. Nifedipine is a calcium channel blocker which is used primarily for the treatment of hypertension, while lovastatin is an HMG CoA reductase inhibitor for the treatment of hypercholesterolemia. Structurally, nifedipine is a dihydropyridine compound and lovastatin is a lactone based structure. The structures of these compounds are set forth below in order to show the dissimilarity of these two agents:



Nifedipine



Lovastatin

Accordingly, as Chen et al. do not teach any preferred species which have structural similarity to lovastatin, there is no motivation therein to one skilled in the art to select lovastatin from the large genus disclosed therein.

Further, any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. *See*, e.g., *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select lovastatin from the genus described therein.

***ii.*) The Examiner has made an impermissible "obvious to try" argument**

In the Office Action, the Examiner stated that "it is obvious to use lovastatin since Chen teaches lovastatin as a suitable drug to use in the controlled release dosage form.

Therefore, the motivation of utilizing lovastatin is within the disclosure of Chen itself."

Applicants submit that the Examiner is applying an improper "obvious to try" rationale in support of the obviousness rejection. In support of this position, the Examiner is directed to MPEP 8th Edition, Revision 4, § 2145 Subsection X (B) which states that "[i]n some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possible arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful..." *See In Re O'Farrell*, 853 F 2.d 894, 903.

Applicants respectfully submit that Chen et al. do not provide any parameters which are critical with respect to a lovastatin dosage form and do not give any direction as to choosing lovastatin from the numerous agents described therein. Therefore, Applicants respectfully submit that the Examiner has made an impermissible "obvious to try" argument in rejecting the present claims.

***iii.*) The Chen controlled release dosage form would not necessarily function the same irrespective of the drug utilized**

In the Office action, the Examiner stated that "a skilled artisan would expect that the Chen's controlled release dosage form would function the same irrespective of the drug utilized since Chen's general discloses is to a controlled release device that provides controlled release of the medicament in order to maintain therapeutic serum levels of the medicament."

Initially, Applicants note that the Examiner appears to be ignoring the T_{max} and bioavailability limitations of the claims and is examining the present claims as if they were simply directed to a controlled release dosage form. In fact, the claims recite specific T_{max} and bioavailability limitations and the claims are not intended to encompass controlled release dosage forms which do not meet these narrow limitations.

It is respectfully submitted that differences physical properties (e.g., solubility and melting point) would be considered in the preparation of a controlled release formulation and one skilled in the art would realize that a controlled release dosage form would not necessarily function the same irrespective of the drug utilized.

Applicants respectfully submit that Chen et al. fail to teach, hint or suggest the T_{max} range recited in the present claims as no information is provided in the reference concerning a desired time to maximum plasma concentration (T_{max}) for any drug, let alone lovastatin. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that a particular T_{max} would be desirable for controlled release formulations containing lovastatin.

Applicants further submit that Chen et al. fail to teach or suggest a controlled release oral solid dosage form which increases the bioavailability of an active agent as compared to the same amount of the active agent administered in an immediate release form as recited in independent claim 76 (with respect to lovastatin). In addition, there is no information contained in Chen et al. regarding any pharmacokinetic values with respect to lovastatin, nor is there any mention of lovastatin acid in Chen et al.

***iv.*) The Examiner is not properly making a determination as to whether the prior art meets the presently claimed limitations**

In the Office Action, the Examiner stated that "the examiner must make a sound rationale as to why the prior art's dosage form is capable of meeting the instantly claimed functional limitations"

In making this statement, it appears that the Examiner is relying on probabilities and possibilities in order to make a prima facie case of obviousness as to the prior art inherently meeting the functional features of the instant claims. Applicants submit that this is not the correct standard for determining whether the claimed features are met by

the prior art. Applicants note that "the inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In Re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995).

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). *See also*, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Applicants respectfully submit that the Examiner cannot state that a lovastatin dosage form prepared in accordance with the description of Chen et al. would necessarily provide a T_{max} of about 10 to about 32 hours as recited in the present claims. For example, one skilled in the art could prepare a lovastatin dosage form in accordance with the teachings of Chen et al. to provide a T_{max} of 3 hours or 5 hours after administration, which would not be meet the limitations of the claims. Therefore, Applicants respectfully submit that the Examiner is relying on probabilities and possibilities in making the rejection and not on what is necessarily present in the prior art.

In order to formulate a lovastatin formulation as recited in the claims of the present invention, one skilled in the art would have to optimize conditions, ingredients and parameters of the formulations described in Chen et al. as the reference does not specifically teach how to formulate lovastatin utilizing their described technology. The means to achieve the optimal conditions for formulating a lovastatin formulation are

neither disclosed explicitly nor implicitly in view of Chen et al. Further, the mere fact that lovastatin can be inserted into one of the formulations of the Barry reference and may provide the functional limitations of the present claims does not rise to the level of inherent obviousness as such functional limitations must be "necessarily present" in lovastatin formulations prepared in view of Chen et al.

The Examiner takes the further position that Table 1 of the present application is similar in structure to the formulations of Chen et al. and that both would function similarly, if not the same. Applicants respectfully disagree with this position. The broad ranges described in the specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that lovastatin formulations could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

***v.)* The Examiner is not properly considering the functional limitations of the present claims**

In the Office Action, the Examiner states that "in instant case, the claims broadly recite a 'controlled release oral dosage form' without any structurally distinguishing features."

In making this statement, the Examiner is not considering the distinguishing functional features of the present claims (i.e., the T_{max} and bioavailability limitations). The Examiner is reminded that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms," and that "functional language does not, in and of itself, render a claim improper." MPEP 8th Edition, Revision 4, § 2173.05(g) (citing *In re Swinehart*, 169 USPQ 226 (CCPA 1971)). In addition, "[a] functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly

conveys to a person of ordinary skill in the pertinent art in the context in which it is used." MPEP 8th Edition, Revision 4, § 2173.05(g).

Therefore, Applicants respectfully submit that consideration of the functional limitations of the claims would distinguish the present claims over Chen et al., which do not teach or suggest the presently claimed T_{max} and bioavailability limitations.

***vi.*) The Examiner is relying on hindsight reasoning**

In the Office Action, the Examiner stated that "hindsight reasoning has not been applied since Chen's disclosure, itself, provide the motivation to utilize lovastatin."

In response, Applicants again point out that the Examiner is not considering the claimed T_{max} and bioavailability limitations of the present claims. The Examiner is solely providing motivation to prepare lovastatin formulations in accordance with Chen et al. (a position in which the Applicants do not agree) and has not provided motivation to prepare a lovastatin formulation which (i) increases the bioavailability of lovastatin and does not increase the bioavailability of lovastatin acid, as compared to the same amount of lovastatin administered in an immediate release dosage form and (ii) provides a time to maximum plasma concentration (T_{max}) at from about 10 to about 32 hours.

Therefore, Applicants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare the presently claimed formulations.

In view of the arguments presented above, Applicants submit that Chen et al. fail to teach or suggest the presently claimed dosage form. Accordingly, it is respectfully requested that the rejection of claims 76-84 and 88-89 under 35 U.S.C. § 103(a) in view of Chen et al. be removed.

2. Rejection over Chen et al. in combination with Cheng et al (hereinafter "the Cheng reference").

***vi.*) The Examiner is relying on hindsight reasoning**

This rejection is traversed. For the reasons stated above, Applicants respectfully submit that Chen et al. fail to teach or suggest the presently claimed controlled release dosage form which:

(1) comprises a therapeutically effective amount of lovastatin;
(2) increases the bioavailability of lovastatin and not increase the bioavailability of lovastatin acid; and
(3) provides a Tmax at from about 10 to about 32 hours.

It was stated in the Office Action that "Cheng is not relied upon to teach the instantly claimed Tmax since it is the examiner's position that Chen's controlled device provides the same Tmax." However, Applicants submit, as previously discussed, that it is improper to draw the conclusion that the structure and formulation of Chen et al. is substantially similar to that of the present invention. Therefore, it is also improper to conclude that the Chen formulation would necessarily possess the claimed pharmacokinetic parameters.

With respect to the Cheng reference, Applicants submit that one of ordinary skill in the art would not be motivated to combine Chen et al., with the Cheng reference, based on mere mention of lovastatin along with 47 other possible medicaments. Even assuming arguendo that there was motivation, the Cheng reference still fails to teach or suggest a controlled release dosage form which:

(2) increases the bioavailability of lovastatin and not increase the bioavailability of lovastatin acid; and
(3) provides a Tmax at from about 10 to about 32 hours.

The Examiner stated "although Cheng teaches that SRT8 and SRT14 were dropped from further testing, nonetheless SRT14 is disclosed as having a higher bioavailability compared to the immediate release dosage form." However, the Examiner has ignored the reason that SRT14 was dropped from further testing "[b]ecause the SRT8 and SRT14 dosage forms showed little evidence of *in vivo* sustained-release functionality." (Emphasis Added). See page 1685 of Cheng et al. As Cheng et al. state that there is little evidence of in-vivo sustained release functionality for SRT14, one skilled in the art would recognize that SRT14 is not a controlled release dosage form and does not cure the deficiencies of Chen et al.

Accordingly, as the Cheng reference fails to cure the deficiencies of Chen et al., Applicants respectfully request that the rejection of claims 76-84 and 88-89 under 35 U.S.C. § 103(a) over Chen et al. in view of the Cheng reference be removed.

C. Double Patenting Rejections

Claims 76-87 were rejected for obviousness-type double patenting over claims 1-12 of U.S. Patent No. 5,916,595, claims 1 and 4-14 of U.S. Patent No. 6,485,748, and claims 1, 4-13, and 15 of U.S. Patent No. 5,837,379.

1. U.S. Patent Nos. 5,916,595

In response to the obviousness-type double patenting rejection over claims 1-12 of U.S. Patent No. 5,916,595, a terminal disclaimer over this patent is filed herewith. Applicants acknowledge that the terminal disclaimer was inadvertently omitted in the last response, and is submitted herewith.

Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

2. U.S. Patent Nos. 6,485,748

The rejection of claim 76-87 over claims 1-12 of U.S. Patent No. 6,485,748 in view of Cheng et al. is traversed.

Applicants respectfully submit that the claims of the '748 patent fail to teach or suggest the presently claimed controlled release dosage form which:

(1) comprises a therapeutically effective amount of lovastatin;
(2) increases the bioavailability of lovastatin and not increasing the bioavailability of lovastatin acid; and
(3) provides a Tmax at from about 10 to about 32 hours.

In the Office Action, it was stated that "Table I of the instant specification provides a general formula that provides the instantly claimed functional limitations" and that "the controlled dosage form of US patent '748 would provide the instantly claimed functional limitation including the instant Tmax". Applicants respectfully disagree with this position. Applicants re-submit that Table I is a guideline by which one of ordinary skill in the art may use to prepare the presently claimed dosage form. However, not every formulation provided for within the guideline will necessarily produce the desired result and the claimed Tmax parameters would be achieved only through optimization.

With respect to the Cheng reference, Applicants submit that the Cheng reference fails to cure the deficiencies of the claims of the '748 patent, as it does not teach or suggest a controlled release dosage form which:

(2) increases the bioavailability of lovastatin and not increase the bioavailability of lovastatin acid; and
(3) provides a Tmax at from about 10 to about 32 hours.

Accordingly, the Examiner is requested to remove the double patenting rejection over the claims of the '748 patent in view of Cheng et al.

3. U.S. Patent No. 5,837,379 (Chen et al.)

The rejection of claim 76-84, 88-89 over claims 1, 4-13, and 15 of U.S. Patent No. 5,837,379 (Chen et al.) in view of Cheng et al. is traversed.

For similar reasons as discussed above with respect to the 35 U.S.C. § 103(a) rejection of the present claims over Chen et al., it is respectfully submitted that the claims of Chen et al. fail to teach or suggest the presently claimed controlled release dosage form which:

(1) comprises a therapeutically effective amount of lovastatin;
(2) increases the bioavailability of lovastatin and not increasing the bioavailability of lovastatin acid; and
(3) provides a Tmax at from about 10 to about 32 hours.

For similar reasons as discussed above with respect to the 35 U.S.C. § 103(a) rejection of the present claims over Chen et al. in view of the Cheng reference, Applicants submit that the Cheng reference fails to cure the deficiencies of the claims of Chen et al.

Accordingly, the Examiner is requested to remove the double patenting rejection over the claims of the '379 patent in view of Cheng et al.

In view of the terminal disclaimer filed herewith with respect to the '595 patent and the arguments presented with respect to the '748 patent and the '379 patent, Applicants respectfully request that these obviousness-type double patenting rejections be removed.

III. Conclusion

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance and expedite prosecution of the present application.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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